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UK CL (Edition N) C2C CZB CZD
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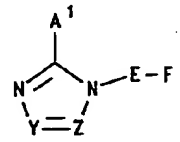
(54) Triazole derivatives

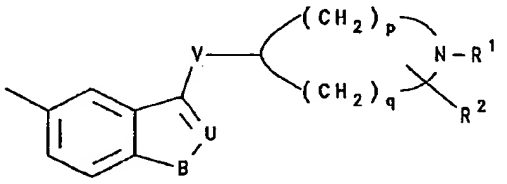
(57) A class of substituted triazole derivatives are selective agonists of 5-HT_1 -like receptors and are therefore useful in the treatment of clinical conditions, in particular migraine and associated disorders, for which a selective agonist of these receptors is indicated. The compounds have the formula:-



(I)

wherein

one of Y and Z represents nitrogen and the other represents C-A^2; E represents a bond or C_{1-4}alkylene;
F represents a group of formula



;

B represents oxygen, sulphur or N-R^3;
U represents nitrogen or C-R4 ;
V represents C_{1-4}alkylene;
p is 0 or 1 and q is 1 to 4 with p+q being 2 to 4;
R^2 is a defined substituent and the remaining symbols represent hydrogen or defined substituents.

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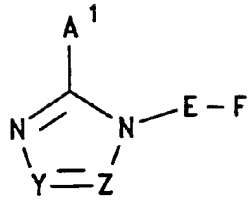
TRIAZOLE DERIVATIVES

The present invention relates to a class of substituted triazole derivatives which act on 5-hydroxytryptamine (5-HT) receptors, being selective agonists of so-called "5-HT_1-like" receptors. They are therefore useful in the treatment of clinical conditions for which a selective agonist of these receptors is indicated.

5-HT_1-like receptor agonists which exhibit selective vasoconstrictor activity have recently been described as being of use in the treatment of migraine (see, for example, A. Doenicke et al., The Lancet, 1988, Vol. 1, 1309-11). The compounds of the present invention, being selective 5-HT_1-like receptor agonists, are accordingly of particular use in the treatment of migraine and associated conditions, e.g. cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, tension headache and paediatric migraine.

WO-A-94/02477, published on 3rd February 1994, describes a class of substituted imidazole, triazole and tetrazole derivatives which are stated to be selective agonists of 5-HT_1-like receptors and hence to be of particular use in the treatment of migraine and associated conditions.

The present invention provides a compound of formula I, or a salt or prodrug thereof:



(I)

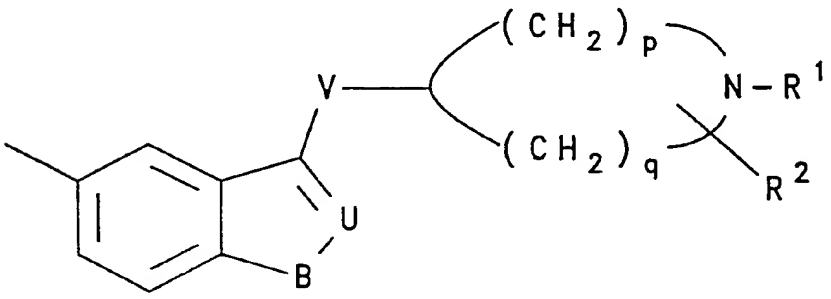
wherein

one of Y and Z represents nitrogen and the other represents C-A^2;

A^1 and A^2 independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, $-OR^X$, $-SR^X$, $-NR^XR^Y$, $-NR^XCOR^Y$, $-NR^XCO_2R^Y$, $-NR^XSO_2R^Y$, or $-NR^ZCTNR^XR^Y$;

E represents a bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

F represents a group of formula



;

B represents oxygen, sulphur or N-R^3;

U represents nitrogen or C-R^4;

V represents a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

p is zero or 1 and q is an integer from 1 to 4, provided that the sum of p+q is 2, 3 or 4;

R^2 represents hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, $-OR^X$, $-SR^X$,

$-NR^XR^Y$, $-NR^XCOR^Y$, $-NR^XCO_2R^Y$, $-NR^XSO_2R^Y$, $-NR^ZCTNR^XR^Y$, $-COR^X$, $-CO_2R^X$, or $-CONR^XR^Y$;

R^1, R^3 and R^4 independently represent hydrogen or C_{1-6} alkyl;

R^X and R^Y independently represent hydrogen, hydrocarbon or a heterocyclic group, or R^X and R^Y together represent a C_{2-6} alkylene group;

R^Z represents hydrogen, hydrocarbon or a heterocyclic group;

T represents oxygen, sulphur or a group of formula =N.G; and

G represents hydrocarbon, a heterocyclic group or an electron-withdrawing group.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing

up to 18 carbon atoms, suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable hydrocarbon groups include C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl and aryl(C_{1-6})alkyl.

The expression "a heterocyclic group" as used herein includes cyclic groups containing up to 18 carbon atoms and at least one heteroatom preferably selected from oxygen, nitrogen and sulphur. The heterocyclic group suitably contains up to 15 carbon atoms and conveniently up to 12 carbon atoms, and is preferably linked through carbon. Examples of suitable heterocyclic groups include C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl and heteroaryl(C_{1-6})alkyl groups.

Suitable alkyl groups include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl and butyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl.

Suitable alkenyl groups include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl and allyl groups.

Suitable alkynyl groups include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl.

A particular aryl group is phenyl.

Particular aryl(C_{1-6})alkyl groups include benzyl, phenethyl and phenylpropyl.

Suitable heterocycloalkyl groups include azetidinyl, pyrrolidyl, piperidyl, piperazinyl and morpholinyl groups.

Suitable heteroaryl groups include pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, imidazolyl, oxadiazolyl and thiadiazolyl groups.

Particular heteroaryl(C_{1-6})alkyl groups include pyridylmethyl and pyrazinylmethyl.

The hydrocarbon and heterocyclic groups may in turn be optionally substituted by one or more groups selected from C_{1-6} alkyl, adamantyl, phenyl, halogen, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, aryloxy, keto, C_{1-3} alkylenedioxy, nitro, cyano, carboxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkoxycarbonyl(C_{1-6})alkyl, C_{2-6} alkylcarbonyloxy, arylcarbonyloxy, C_{2-6} alkylcarbonyl, arylcarbonyl, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, arylsulphonyl, $-NR^VR^W$, $-NR^VCOR^W$, $-NR^VCO_2R^W$, $-NR^VSO_2R^W$, $-CH_2NR^VSO_2R^W$, $-NHCONR^VR^W$, $-CONR^VR^W$, $-SO_2NR^VR^W$ and $-CH_2SO_2NR^VR^W$, in which R^V and R^W independently represent hydrogen, C_{1-6} alkyl, aryl or aryl(C_{1-6})alkyl, or R^V and R^W together represent a C_{2-6} alkylene group.

When R^X and R^Y, or R^V and R^W, together represent a C_{2-6} alkylene group, this group may be an ethylene, propylene, butylene, pentamethylene or hexamethylene group, preferably butylene or pentamethylene.

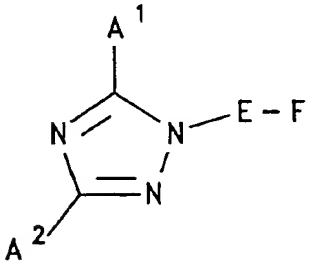
When the group G represents an electron-withdrawing group, this group is suitably cyano, nitro, $-COR^X$, $-CO_2R^X$ or $-SO_2R^X$, in which R^X is as defined above.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine.

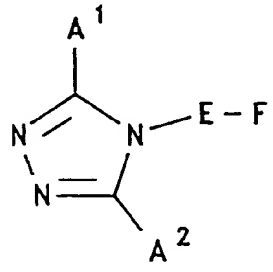
The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible in vivo into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

It will be appreciated that the triazole rings of formula I can exist as isomeric forms having differing substitution patterns. These may suitably be represented by formulae IA and IB as follows:



(IA)



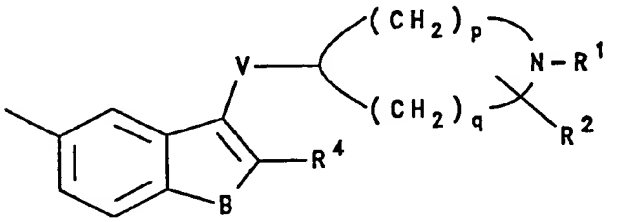
(IB)

wherein A^1, A^2, E and F are as defined above.

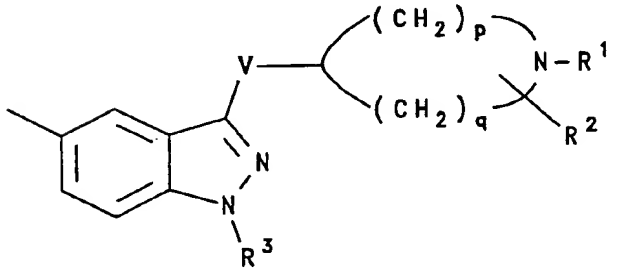
The alkylene chains E and V may be, for example, methylene, ethylene, 1-methylethylene, propylene or 2-methylpropylene. Alternatively, the group E may represent a single bond such that the group F in formula I is attached directly to the triazole ring.

Suitably, V represents a methylene chain.

The group F is suitably an indole, benzofuran or benzthiophene moiety of formula FA, or an indazole moiety of formula FB:

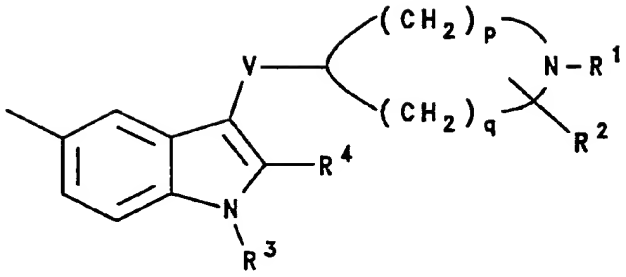


(FA)



(FB)

wherein B, V, p, q, R^1, R^2, R^3 and R^4 are as defined above. Preferably, the group F represents an indole moiety of structure FC:



(FC)

wherein V, p, q, R^1, R^2, R^3 and R^4 are as defined above, in particular wherein R^3 and R^4 are both hydrogen.

Suitable values for the groups A^1, A^2 and R^2 include C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, C_{1-6} alkoxy or C_{1-6} alkylthio, any of which groups may be optionally substituted; and halogen, cyano, trifluoromethyl or $-NR^xR^y$, in which R^x and R^y are as defined above. In addition, one or both of A^1 and A^2 may represent hydrogen. Examples of optional substituents on the groups A^1, A^2 and R^2 suitably include trifluoromethyl, C_{1-6} alkoxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkylcarbonyl, C_{1-6} alkylsulphonyl, arylsulphonyl, amino, mono- or di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino, arylcarbonylamino, C_{2-6} alkoxycarbonylamino, C_{1-6} alkylsulphonylamino, arylsulphonylamino, C_{1-6} alkylsulphonylaminomethyl, aminocarbonylamino, mono- or di(C_{1-6})alkylaminocarbonylamino, mono- or diarylaminocarbonylamino, pyrrolidylcarbonylamino, aminocarbonyl, mono- or di(C_{1-6})alkylaminocarbonyl, C_{1-6} alkylaminosulphonyl, aminosulphonylmethyl, and mono- or di(C_{1-6})alkylaminosulphonylmethyl.

Particular values of A^1, A^2 and R^2 include methyl, methoxymethyl, aminomethyl, dimethylaminomethyl,

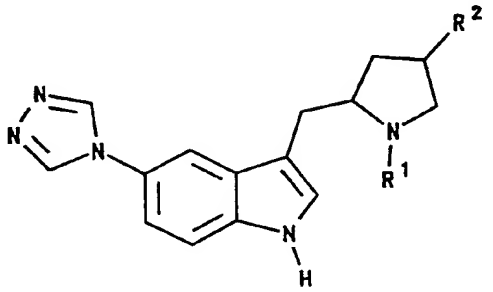
acetylaminomethyl, benzoylaminomethyl, t-butoxycarbonylaminomethyl, methylsulphonylaminomethyl, phenylsulphonylaminomethyl, aminocarbonylmethyl, ethyl, aminoethyl, acetylaminoethyl, benzoylaminoethyl, methoxycarbonylaminoethyl, ethoxycarbonylaminoethyl, t-butoxycarbonylaminoethyl, methylsulphonylaminoethyl, aminocarbonylaminoethyl, methylaminocarbonylaminoethyl, t-butylaminocarbonyl-aminoethyl, phenylaminocarbonylaminoethyl, pyrrolidylcarbonylaminoethyl, cyclopropyl, phenyl, methylsulphonylaminophenyl, aminocarbonylphenyl, methylaminocarbonylphenyl, methylsulphonylaminomethyl-phenyl, aminosulphonylmethylphenyl, methylaminosulphonyl-methylphenyl, dimethylaminosulphonylmethylphenyl, benzyl, trifluoromethylbenzyl, methoxybenzyl, acetylaminobenzyl, methylsulphonylaminobenzyl, aminocarbonylaminobenzyl, aminocarbonylbenzyl, methylaminocarbonylbenzyl, methylsulphonylbenzyl, methylaminosulphonylbenzyl, pyridylmethyl, methoxypyridylmethyl, amino, methylamino, benzylamino, dimethylamino, t-butoxycarbonylamino-ethylamino and methylsulphonylaminoethylamino. In addition, one or both of A^1 and A^2 may represent hydrogen.

Preferred values of A^1 and A^2 include hydrogen, methyl and ethyl.

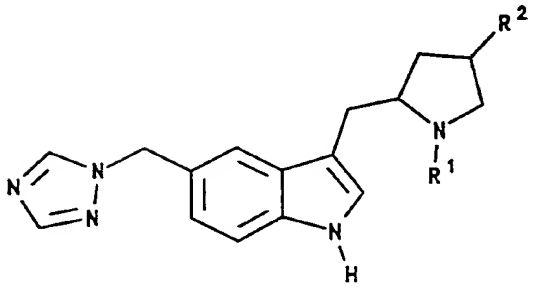
The heterocyclic ring containing the moiety $N-R^1$ is an azetidin-2-yl, azetidin-3-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-2-yl or piperidin-3-yl ring, in particular an azetidin-2-yl or pyrrolidin-2-yl ring, substituted on the ring nitrogen atom by the group R^1.

Preferred values for the groups R^1, R^3 and R^4 include hydrogen and methyl.

Particular sub-classes of compounds according to the invention are represented by the compounds of formulae IIA and IIB, and salts and prodrugs thereof:



(IIA)



(IIB)

wherein R^1 and R^2 are as defined with reference to formula I above.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a

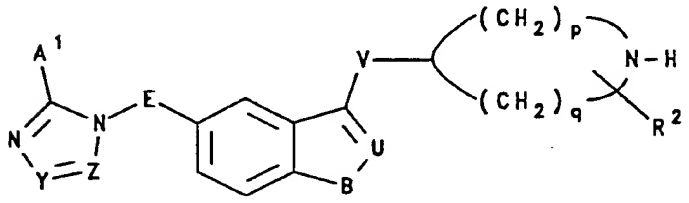
pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous

solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of migraine, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The compounds according to this invention may be prepared by a process which comprises reacting a compound of formula III with a compound of formula IV:



(III)

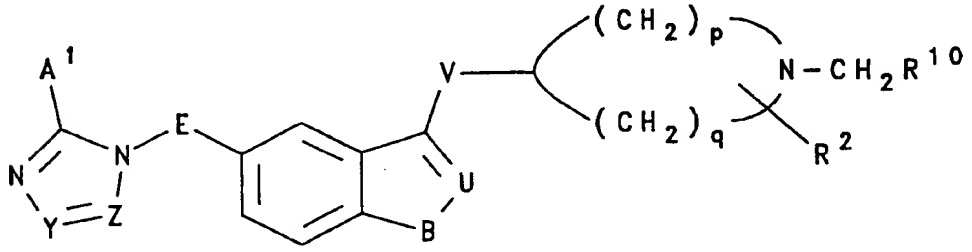
(IV)

wherein A^1, Y, Z, E, B, U, V, p, q, R^1 and R^2 are as defined above, and L represents a suitable leaving group.

The leaving group L is suitably a halogen atom, e.g. bromine or iodine.

The reaction is conveniently carried out by stirring the reactants under basic conditions in a suitable solvent, for example in a dimethoxyethane and N,N-dimethylformamide solvent system in the presence of sodium carbonate, typically at the reflux temperature of the solvent.

In an alternative procedure, the compounds according to the invention represented by formula V:

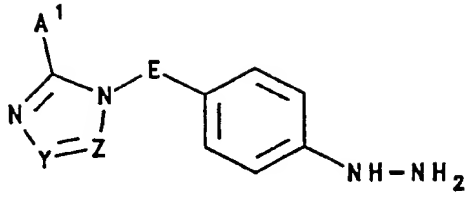


(V)

wherein A^1, Y, Z, E, B, U, V, p, q and R^2 are as defined above, and $-CH_2R^{10}$ corresponds to a group of formula R^1 as defined above; may be prepared by a reductive amination process which comprises reacting a compound of formula III as defined above with an aldehyde derivative of formula R^{10}-CHO in the presence of a reducing agent.

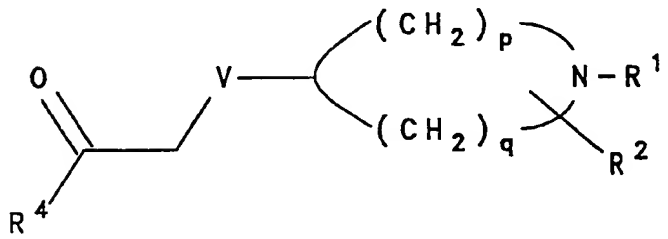
An appropriate reducing agent for use in this procedure is sodium cyanoborohydride, in which case the reaction is conveniently carried out in an alcoholic solvent such as methanol, typically in the presence of acetic acid.

In a further procedure, the compounds according to the invention wherein the group F is an indole moiety of structure FC as defined above may be prepared by reacting a compound of formula VI:



(VI)

wherein A^1, Y, Z and E are as defined above; with a compound of formula VII or a carbonyl-protected form thereof:

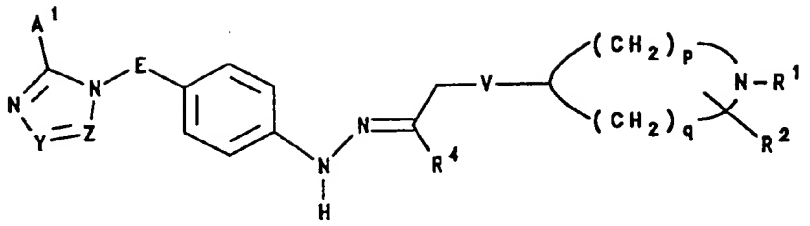


(VII)

wherein V, p, q, R^1, R^2 and R^4 are as defined above; and subsequently, where required, N-alkylation by standard methods to introduce the moiety R^3.

Suitable carbonyl-protected forms of the compounds of formula VII include the dimethyl acetal or ketal derivatives.

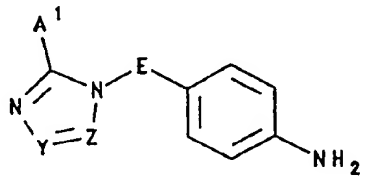
The reaction of compounds VI and VII may be carried out in a single step (Fischer indole synthesis) or by an initial non-cyclising step at a lower temperature to give a compound of formula VIII:



(VIII)

wherein A^1, Y, Z, E, V, p, q, R^1, R^2 and R^4 are as defined above; followed by cyclisation using a suitable reagent, such as a polyphosphate ester.

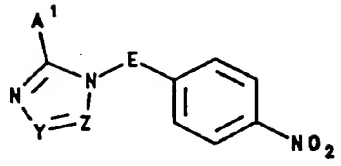
The hydrazines of formula VI may be prepared from the corresponding anilines of formula IX:



(IX)

wherein A^1, Y, Z and E are as defined above; by diazotisation followed by reduction. Diazotisation is typically carried out using sodium nitrite/conc. HCl and the resulting diazo product reduced <u>in situ</u> using, for example, tin(II) chloride/conc. HCl, sodium sulphite/conc. HCl, or sodium sulphite/conc. H_2SO_4.

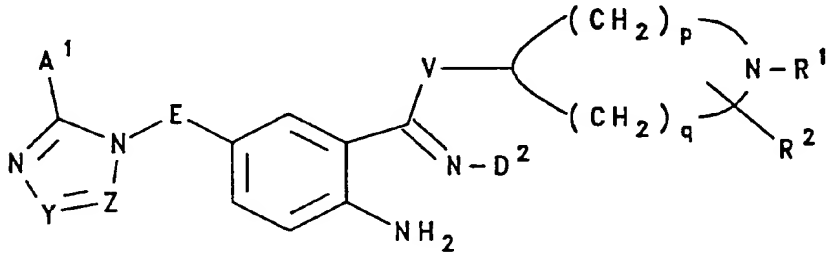
The anilines of formula IX may be prepared by reduction of the corresponding nitro compounds of formula X:



(X)

wherein A^1, Y, Z and E are as defined above; typically by transfer hydrogenation using a hydrogenation catalyst such as palladium on charcoal in the presence of a hydrogen donor such as ammonium formate, or alternatively by conventional catalytic hydrogenation or using tin(II) chloride.

In a still further process, the compounds according to the invention wherein the group F is an indazole moiety of structure FB as defined above may be prepared by the cyclisation of a compound of formula XI:



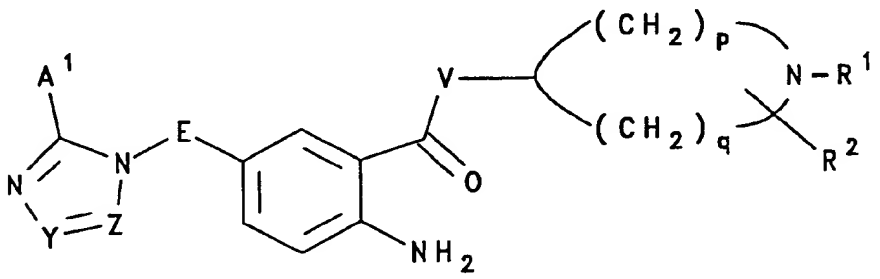
(XI)

wherein A^1, Y, Z, E, V, p, q, R^1 and R^2 are as defined above and D^2 represents a readily displaceable group; and subsequently, where required, N-alkylation by standard methods to introduce the moiety R^3.

The cyclisation of compound XI is conveniently achieved in a suitable organic solvent at an elevated

temperature, for example in a mixture of m-xylene and 2,6-lutidine at a temperature in the region of 140°C.

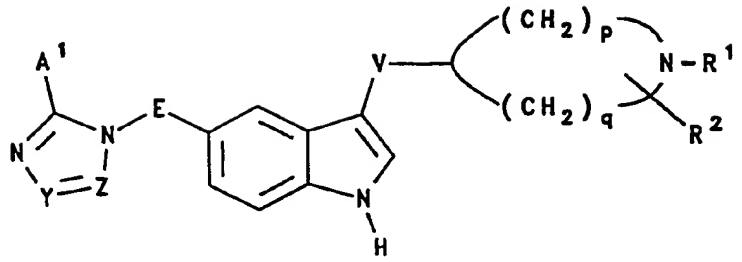
The readily displaceable group D^2 in the compounds of formula XI suitably represents a C_{1-4} alkanoyloxy group, preferably acetoxy. Where D^2 in the desired compound of formula XI represents acetoxy, this compound may be conveniently prepared by treating a carbonyl compound of formula XII:



(XII)

wherein A^1, Y, Z, E, V, p, q, R^1 and R^2 are as defined above; or a protected derivative thereof; with hydroxylamine hydrochloride, advantageously in pyridine at the reflux temperature of the solvent; followed by acetylation with acetic anhydride, advantageously in the presence of a catalytic quantity of 4-dimethylaminopyridine, in dichloromethane at room temperature.

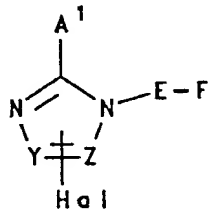
The N-formyl protected derivative of the intermediate of formula XII may be conveniently prepared by ozonolysis of an indole derivative of formula XIII:



(XIII)

wherein A^1, Y, Z, E, V, p, q, R^1 and R^2 are as defined above; followed by a reductive work-up, advantageously using dimethylsulphide.

In an alternative process, the triazole compounds according to the invention may be prepared by a method which comprises reacting a compound of formula XIV:



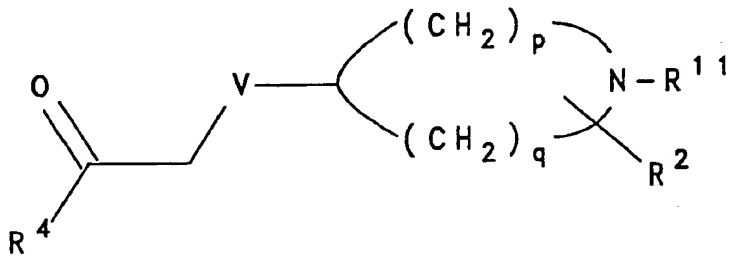
(XIV)

wherein A^1, Y, Z, E and F are as defined above, and Hal represents halogen; with a reagent which provides an anion $^-A^2$, where A^2 is as previously defined.

Reagents which may provide the anion $^-A^2$ include Grignard reagents A^2MgHal (where Hal = halogen); organocuprate reagents such as $LiA^2{}_2Cu$; organolithium reagents A^2Li; or compounds which stabilise the anion by means of an adjacent activating group such as an ester or enolisable ketone function. In this case, the adjacent

ester or ketone function may be retained after the process is complete, or may be removed. For example, an ester moiety may be hydrolysed and decarboxylated.

The compounds of formula III above may be prepared by reacting a compound of formula VI as defined above with a compound of formula XV, or a carbonyl-protected form thereof:



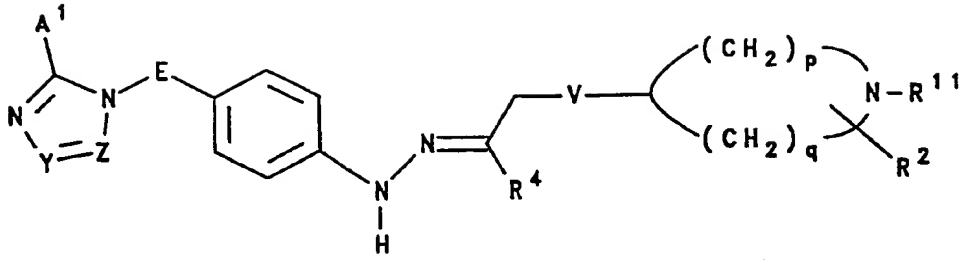
(XV)

wherein V, p, q, R^2 and R^4 are as defined above, and R^{11} represents hydrogen or an amino-protecting group; followed, where required, by removal of the amino-protecting group R^{11}.

As for compound VII, suitable carbonyl-protected forms of the compounds of formula XV include the dimethyl acetal and ketal derivatives.

The amino-protecting group R^{11}, where present, is suitably a lower alkoxycarbonyl moiety such as t-butoxycarbonyl (BOC), which can be conveniently removed as necessary by treatment with acid.

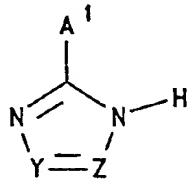
As with that between compounds VI and VII, the reaction between compounds VI and XV may be carried out in a single step (Fischer indole synthesis) or by an initial non-cyclising step at a lower temperature to give a compound of formula XVI:



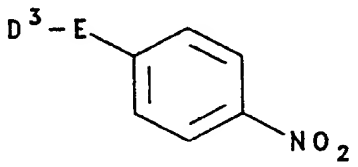
(XVI)

wherein Y, Z, A^1, E, V, p, q, R^2, R^4 and R^{11} are as defined above; followed by cyclisation using a suitable reagent, e.g. a polyphosphate ester.

The nitro compounds of formula X may be prepared by a variety of methods which will be readily apparent to those skilled in the art. For example, the relevant compounds of formula X may be prepared by reacting the anion of a compound of formula XVII with a compound of formula XVIII:



(XVII)



(XVIII)

wherein Y, Z, A^1 and E are as defined above, and D^3 represents a readily displaceable group.

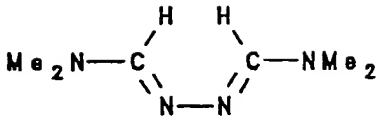
The anion of compound XVII may be generated by carrying out the reaction in a base such as triethylamine. Where salts of the compounds of formula XVII are commercially available, e.g. the sodium salt of 1,2,4-triazole, these are advantageously utilised in N,N-

dimethylformamide solution in place of the compounds of formula XVII themselves, with no requirement in this instance for additional base to be present in the reaction mixture.

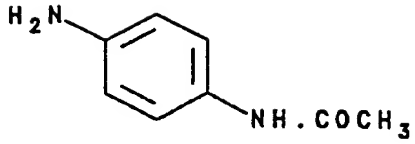
The readily displaceable group D^3 in the compounds of formula XVIII is suitably a halogen atom, preferably bromine; except when the moiety D^3 is attached directly to the aromatic ring, i.e. when E represents a bond, in which case D^3 is preferably fluorine.

In an alternative approach, the compounds of formula X wherein the five-membered heteroaromatic ring is a 1,2,4-triazol-1-yl moiety and A^1 and A^2 are both hydrogen may be prepared by reacting 4-amino-1,2,4-triazole with a compound of formula XVIII as defined above, followed by deamination of the resulting 1-substituted 4-amino-4H-1,2,4-triazolium salt by treatment with nitrous acid and subsequent neutralisation. This transformation, which may be accomplished in two separate steps or advantageously as a "one-pot" procedure with both steps combined, is conveniently effected using reaction conditions analogous to those described in J. Org. Chem., 1989, 54, 731.

Following a further representative pathway, the aniline derivatives of formula IX wherein the five-membered heteroaromatic ring is a 1,2,4-triazol-4-yl moiety, E is a bond and A^1 and A^2 are both hydrogen may be prepared by reacting the hydrazine derivative of formula XIX with the acetanilide of formula XX:



(XIX)



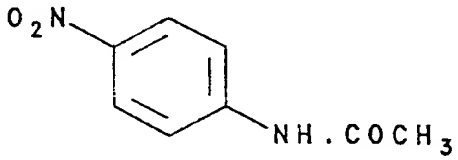
(XX)

followed by removal of the N-acetyl protecting group.

The reaction between compounds XIX and XX is conveniently effected in refluxing toluene, advantageously in the presence of a catalytic quantity of p-toluenesulphonic acid. Subsequent removal of the N-acetyl protecting group is typically effected in hot aqueous 5N hydrochloric acid.

The hydrazine derivative of formula XIX can be prepared from N,N'-diformylhydrazine by reaction with thionyl chloride/N,N-dimethylformamide, as reported in J. Chem. Soc. (C), 1967, 1664, and subsequent treatment with sodium methoxide in methanol.

The acetanilide of formula XX may be prepared by reduction of the corresponding nitro compound of formula XXI:

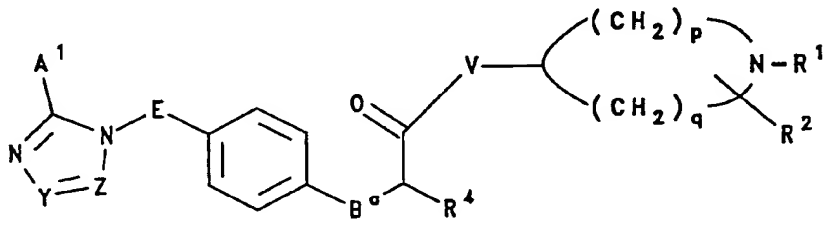


(XXI)

typically by transfer hydrogenation using a hydrogenation catalyst in the presence of a hydrogen donor such as ammonium formate, or alternatively by conventional catalytic hydrogenation or using tin(II) chloride.

The nitro compound of formula XXI is commercially available from the Aldrich Chemical Company Ltd., Gillingham, United Kingdom.

In a yet further process, the compounds according to the invention wherein the group F is a benzofuran or benzthiophene moiety may be prepared by a method which comprises cyclising a compound of formula XXII:

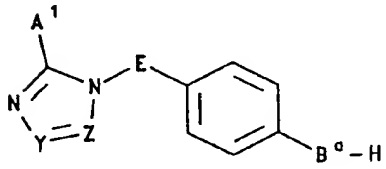


(XXII)

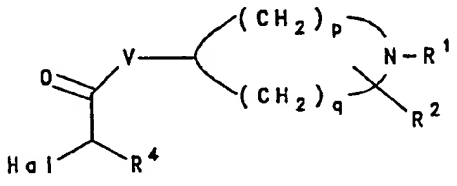
wherein Y, Z, A^1, E, V, p, q, R^1, R^2 and R^4 are as defined above, and B^a represents oxygen or sulphur.

The cyclisation is conveniently effected by using polyphosphoric acid or a polyphosphate ester, advantageously at an elevated temperature.

The compounds of formula XXII may be prepared by reacting a compound of formula XXIII with a compound of formula XXIV:



(XXIII)

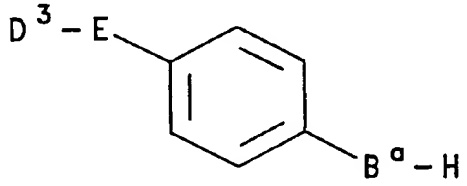


(XXIV)

wherein Y, Z, A^1, E, B^a, V, p, q, R^1, R^2 and R^4 are as defined above, and Hal represents halogen.

The reaction is conveniently effected in the presence of a base such as sodium hydroxide.

The hydroxy and mercapto derivatives of formula XXIII may be prepared by a variety of methods which will be readily apparent to those skilled in the art. In one such method, the anion of a compound of formula XVII as defined above is reacted with a compound of formula XXV:



(XXV)

wherein D^3, E and B^a are as defined above.

The compounds of formula IV, R^{10}-CHO, VII, XV, XVIII, XXIV and XXV, where they are not commercially available, may be prepared by standard procedures well known in the art.

It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I by techniques known from the art. Indeed, as will be appreciated, the compounds of formula III, XIII and XIV, utilised as intermediates in the above-described processes, are compounds according to the invention in their own right. In particular, a compound of formula I wherein R^3 is hydrogen initially obtained may be converted into a compound of formula I wherein R^3 represents C_{1-6} alkyl by standard alkylation techniques, for example by treatment with an alkyl iodide, e.g. methyl iodide, typically under basic conditions, e.g.

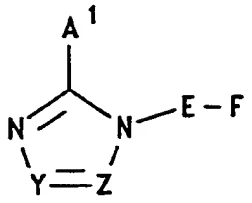
sodium hydride in dimethylformamide, or triethylamine in acetonitrile.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid, followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

CLAIMS:

1. A compound of formula I, or a salt or prodrug thereof:



(I)

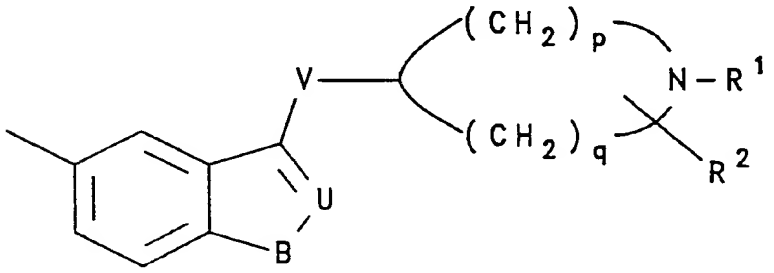
wherein

one of Y and Z represents nitrogen and the other represents C-A^2;

A^1 and A^2 independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, $-OR^x$, $-SR^x$, $-NR^xR^y$, $-NR^xCOR^y$, $-NR^xCO_2R^y$, $-NR^xSO_2R^y$, or $-NR^zCTNR^xR^y$;

E represents a bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

F represents a group of formula



;

B represents oxygen, sulphur or N-R^3;

U represents nitrogen or C-R^4;

V represents a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

p is zero or 1 and q is an integer from 1 to 4, provided that the sum of p+q is 2, 3 or 4;

R^2 represents hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, $-OR^x$, $-SR^x$, $-NR^xR^y$, $-NR^xCOR^y$, $-NR^xCO_2R^y$, $-NR^xSO_2R^y$, $-NR^zCTNR^xR^y$, $-COR^x$, $-CO_2R^x$, or $-CONR^xR^y$;

R^1, R^3 and R^4 independently represent hydrogen or C_{1-6} alkyl;

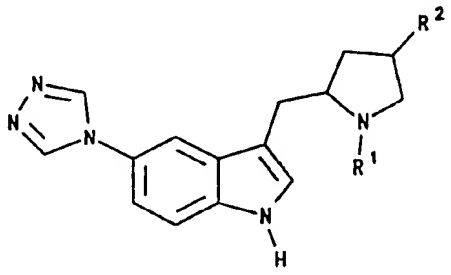
R^x and R^y independently represent hydrogen, hydrocarbon or a heterocyclic group, or R^x and R^y together represent a C_{2-6} alkylene group;

R^z represents hydrogen, hydrocarbon or a heterocyclic group;

T represents oxygen, sulphur or a group of formula =N.G; and

G represents hydrocarbon, a heterocyclic group or an electron-withdrawing group.

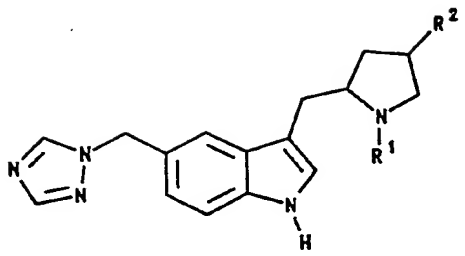
2. A compound as claimed in claim 1 represented by formula IIA, and salts and prodrugs thereof:



(IIA)

wherein R^1 and R^2 are as defined in claim 1.

3. A compound as claimed in claim 1 represented by formula IIB, and salts and prodrugs thereof:



(IIB)

wherein R^1 and R^2 are as defined in claim 1.

4. A compound as claimed in any one of the preceding claims wherein R^1 is hydrogen or methyl.

5. A pharmaceutical composition comprising a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof or a prodrug thereof in association with a pharmaceutically acceptable carrier.

6. The use of a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof or a prodrug thereof for the manufacture of a medicament for the treatment and/or prevention of clinical conditions for which a selective agonist of 5-HT_1-like receptors is indicated.

Patents Act 1977
Examiner's report to the Comptroller under Section 17
(The Search report)

Application number
GB 9501310.8

Relevant Technical Fields

(i) UK Cl (Ed.N) C2C (CZB, CZD)

(ii) Int Cl (Ed.6) C07D

Search Examiner
D S LUCAS

Date of completion of Search
9 MARCH 1995

Databases (see below)
(i) UK Patent Office collections of GB, EP, WO and US patent specifications.

(ii) ONLINE: CAS ONLINE

Documents considered relevant following a search in respect of Claims :-
1-6

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages		Relevant to claim(s)
X, P	WO 94/02477 A	(MERCK SHARP & DOHME) see formual (1) in Claim 1 wherein R' is (ii) and several of the Examples	1-6

Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).